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10/559,814	04/04/2006	Mark B. Pepys	674599-2004	8207

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EXAMINER	
LI, RUIXIANG	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,814	PEPYS ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/08/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/21/2007, 12/23/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Restriction/Election

1. Applicant's election with traverse of Group I and species (R)-1-[6-[(R]-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) in the reply filed on 12/01/2008 is acknowledged. The traversal is on the ground(s) that the claims of Groups I-II all recite the technical feature of the treatment or prevention of osteoarthritis comprising administering to the subject a therapeutically effective amount of a medicament comprising an agent capable of inhibiting serum amyloid P component (SAP) ligand binding activity or depleting SAP from the plasma of the subject, which is not taught by either Askarov or Briton. Applicants argue that the office action fails to state, and the cited references fails to show, that either chondroitin sulphate or heparin are capable of inhibiting SAP ligand binding activity or depleting SAP from the plasma. Applicants argue that what is not disclosed in Brion is that SAP is a therapeutic target or that the use of chondroitin sulphate in any way interacts with SAP. Applicants argue that chondroitin sulphate is not capable of inhibiting SAP ligand binding in vivo or depleting SAP from the plasma of a subject in vivo. That is chondroitin sulphate is not bound by SAP with sufficient affinity or specificity, if indeed it is bound at all by SAP in whole plasma, to be effective in vivo. Applicants argue that nothing in the cited reference would provide concentrations of chondroitin sulphate which would be effective to inhibit binding of SAP to ligands in vivo, as is required by the special technical feature.

With respect to the reference of Askarov, Applicants argue that the use of heparin as an agent to treat or provide symptomatic relief in osteoarthritis is thus completely inconceivable in actual clinical practice. Applicants argue that heparin, like chondroitin sulphate, is not bound by SAP in plasma with sufficient affinity or specificity to be effective in modifying SAP function in vivo. Applicants argue that heparin and its various factions of different molecular weight are instantly bound with extremely high affinity and avidity by anti-thrombin III in plasma. Applicants argue also that there is no reason to justify disregarding the findings of the International Preliminary Examining Authority regarding unity of invention. Applicants argue that the compounds of Formula I–A and I-B satisfy the unity of invention requirement of PCT Rule 13.2. Applicants further argue that enforcing the present invention requirement and species election would result in inefficiencies and unnecessary expenditures by both the Applicants and the PTO. Applicants argue that the search and examination of each group is likely to be co-extensive and, in any event, would involve such interrelated art such that the search and examination of the entire application can and should be made.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, the independent claim 13 is drawn to a method for treatment or prevention of osteoarthritis in a subject, which comprises administering to the subject a therapeutically effective amount of a medicament comprising an agent capable of inhibiting SAP ligand binding activity or depleting SAP from the plasma of the subject. The claim does not require any particular

structure feature for the agent to be administered. The claim does not limit the agent to be the D- proline of Formula I–A and I-B.

Secondly, the claim only requires administering to a subject a therapeutically effective amount of a medicament to treat osteoarthritis, said medicament comprises an agent that is capable of inhibiting SAP ligand binding or depleting SAP from the plasma of the subject. The cited prior art teaches treatment of osteoarthritis comprises administering an affective amount of either chondroitin sulphate or heparin. Since chondroitin sulphate or heparin is well known in the art to bind SAP, chondroitin sulphate or heparin is necessarily capable of inhibiting ligand binding activity of SAP. Applicants argument that heparin and chondroitin sulphate are not bound by SAP in plasma with sufficient affinity or specificity to be effective in modifying SAP function in vivo is not persuasive because the claim does not require that an agent inhibits SAP ligand binding activity in the presence of plasma, and there is no evidence provided that supports Applicants' argument. Likewise, Applicants argument that the use of heparin as an agent to treat or provide symptomatic relief in osteoarthritis is completely inconceivable in actual clinical practice is only based upon Applicants opinions. There is no evidence provided showing that the teachings of Askarov et al. is wrong and there is no evidence provided so that the examiner would be able to judge the validity of Applicants argument.

Moreover, the opinion of the International Preliminary Examining Authority regarding unity of invention does not prohibit the examiner to make lack of unity

among the inventions when is deemed proper. Furthermore, search and examination of both groups and without species election would place an undue burden on the examiner.

Accordingly, Groups I-II are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept. Thus, unity of invention is lacking and restriction is appropriate.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 13-27 are pending and under consideration.

Information Disclosure Statement

3. The information disclosure statements filed on 10/23/2008 and 06/21/2007 have been considered by the Examiner and a signed copy of the form PTO-1449 is attached to the office action.

Drawings

4. The drawings filed on 12/08/2005 are accepted by the Examiner.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections—35 USC § 112, 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 13-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treatment of osteoarthritis in a subject, comprising administering to the subject a therapeutically effective amount of a medicament comprising (R)-1-[6-[(R]-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC or Ro-63-8695), does not reasonably provide enablement for (i) a method for prevention of osteoarthritis in a subject, comprising administering to the subject a therapeutically effective amount of a medicament comprising CPHPC; and (ii) a method for treatment or prevention of osteoarthritis in a subject, comprising administering to the subject a therapeutically effective amount of a medicament comprising an agent or a substituted or unsubstituted D-proline or stereoanalogue thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int.

1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The breadth of the claims. Claim 13 is drawn to a method for treatment or prevention of osteoarthritis in a subject, which comprises administering to the subject a therapeutically effective amount of a medicament comprising an agent capable of inhibiting SAP ligand binding activity or depleting SAP from the plasma of the subject. Its dependent claims limit the scope of the genus of agents by reciting various limitations. Claim 27 is drawn to a method of prevention of osteoarthritis in a subject, which comprises administering to the subject a therapeutically effective amount of a medicament comprising a substituted or unsubstituted D-proline or stereoanalogue thereof. There is no functional limitation recited in the claim. Thus, the claims are broad because they are drawn to a method comprising administration of a genus of structurally undefined agents in a subject to treat or prevent osteoarthritis.

Nature of the invention and the state of the prior art. The present invention is directed to a method of treating osteoarthritis. WO 95/05394 discloses a molecule that inhibits the binding of SAP to amyloid fibrils, MOβDG (page 2, line 6; Example 1) and an anti-mouse SAP antibody that depletes SAP in mice (Example 3). EP0915088 A1 discloses D-proline derivatives of Formula I-A and I-B (claim 1) that may be used in the treatment of amyloidosis. US Patent No. 7,045,499 B2 teaches that CPHPC specifically targets SAP in vivo, through the specific ligand binding capacity of SAP, and causes aggregation of native pentameric SAP molecules into decameric drug SAP complexes that are then promptly cleared by the liver (column 13, the 4th paragraph). There are no teachings in the art that an artisan could

potentially use to make and use *the claimed genus* of agents.

The amount of direction or guidance presented and the existence of working examples. The specification discloses a class of D-prolines of formula I-A or I-B (page 9). The specification also discloses that D-proline compounds that are capable of inhibiting SAP ligand binding activity or depleting SAP from the plasma of a subject may be obtainable by screening methods disclosed in the specification. The specification further discloses certain D-proline compounds that inhibit SAP ligand binding (Tables 1-III). However, the specification only discloses the treatment of two patients with osteoarthritis with CPHPC (Example G). The specification fails to disclose any other D-proline compounds that deplete SAP from the plasma of the subject and, more importantly, can be used to treat osteoarthritis in a subject. Furthermore, there is no evidence showing that such a treatment would prevent osteoarthritis in a subject.

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary. While the prior art teaches compounds, including D-proline compounds, which may be used in the treatment of amyloidosis, there is no teaching with respect to treating osteoarthritis with theses compounds. It is unpredictable whether an agent, such as a D-proline compound, that can be used in the treatment or prevention of osteoarthritis. It would require large quantity of experimentation for one skilled in the art to determine whether a given agent inhibits SAP ligand binding activity, depletes SAP from the plasma of a subject, or more importantly is useful for treating osteoarthritis in a

subject.

Accordingly, while being enabling for a method for treatment of osteoarthritis in a subject, comprising administering to the subject a therapeutically effective amount of a medicament comprising CPHPC, does not reasonably provide enablement for the instantly claimed method. Thus, it would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

8. Claims 13-24 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claim 13 is drawn to a method for treatment or prevention of osteoarthritis in a subject, which comprises administering to the subject a therapeutically effective amount of a medicament comprising an agent capable of inhibiting SAP ligand binding activity or depleting SAP from the plasma of the subject. Its dependent claims limit the scope of the genus of agents by reciting various limitations. Claim 27 is

drawn to a method of prevention of osteoarthritis in a subject, which comprises administering to the subject a therapeutically effective amount of a medicament comprising a substituted or unsubstituted D-proline or stereoanalogue thereof. Thus, the claims are drawn to a method comprising administration of a genus of structurally undefined agents in a subject to treat or prevent osteoarthritis.

The specification discloses a class of D-prolines of formula I-A or I-B (page 9). In particular, the specification discloses the successful treatment of two patients with osteoarthritis with (R)-1-[6-[(R]-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC; Example G). However, such a disclosure is not adequate to support the broad genus of agents encompassed in the claims because the disclosed species are not sufficiently representative of the genus of agents encompassed in the instant claims. The specification fails to provide any critical structural feature to adequately describe the broad genus of agents that may be administered in the claimed method.

WO 95/05394 discloses a molecule that inhibits the binding of SAP to amyloid fibrils, MOβDG (page 2, line 6; Example 1) and an anti-mouse SAP antibody that depletes SAP in mice (Example 3). EP0915088 A1 discloses D-proline derivatives of Formula I-A and I-B (claim 1) that may be used in the treatment of amyloidosis. US Patent No. 7,045,499 B2 teaches that (R)-1-[6-[(R]-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) specifically targets SAP in vivo, through the specific ligand binding capacity of SAP, and causes aggregation of native pentameric SAP molecules into decameric drug SAP complexes that are then

promptly cleared by the liver (column 13, the 4th paragraph). However, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed agents.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of the agents, and therefore conception is not achieved until reduction to practice has occurred.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the genus of agents encompassed in the claims and thus the instantly claimed methods.

Claim Rejections—35 USC §102 (b)

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 13 and 14 are are rejected under 35 U.S.C. 102(b) as being anticipated by Brion et al. (Osteoarthritis, Oxford Textbook of Medicine, 4th Ed., Vol. 3 (Warrell et al. eds.), Oxford University Press, Oxford, pp.62-68, January, 2003), as evidenced by Danielsen et al. (Biochimica et Biophysica Acta 1339:73-78, 1997).

Brion et al. teach treating osteoarthritis in a subject with chondroitin sulphate (page 67, bottom of left column). Since chondroitin sulphate is well known in the art to bind to SAP as evidenced by Danielsen et al. (see, e.g., Figure 1), chondroitin sulphate or heparin is necessarily capable of inhibiting ligand binding activity of SAP. Thus, the teachings of Brion et al. meet the limitations of claims 13 and 14.

Claim Objection—Minor Informalities

11. Claims 13-25 and 27 are objected to because they recite non-elected subject matter. Appropriate correction is required.

Conclusion

12. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/
Primary Examiner, Art Unit 1646

Ruixiang Li, Ph.D.
March 2, 2009